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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,881	09/11/2003	Harlan W. Waksal	11245/46403	8515
26646 7590 03/27/2007 KENYON & KENYON LLP ONE BROADWAY NEW YORK, NY 10004			EXAMINER HOLLERAN, ANNE L	
			ART UNIT	PAPER NUMBER
			1643	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		03/27/2007	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

10/661,881

Applicant(s)

WAKSAL ET AL

Examiner

Anne L. Holleran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3,24 and 31-48 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,24 and 31-48 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 6/26/06; 6/28/06.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date: \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

1. The amendment filed 1/3/2007 is acknowledged. Claims 2 and 30 were canceled.

Claims 40-48 were added.

Claims 1, 3, 24 and 31-48 are pending and examined on the merits.

#### ***Claim Rejections Withdrawn:***

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. The rejection of claims 1-3, 24 and 30-39 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

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3. The rejection of claims 1 and 30 under 35 U.S.C. 102(e) as being anticipated by Greene (U.S. 6,417,168; issued Jul. 9, 2002; effective filing date Mar. 4, 1998) is withdrawn in view of the amendment to the claims.

4. The rejection of claims 1 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Arnold (U.S. 5,736,534; issued April 7, 1998; effective filing date July, 29, 1996; cited in the IDS) is withdrawn in view of the amendment to the claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The rejection of claims 1-3, 24, and 31-39 under 35 U.S.C. 103(a) as being unpatentable over Saleh (Saleh, M. et al., Proceedings of the American association for Cancer Research, 37: 612, Abstract #4197, 1996, March; cited in the IDS) in view Goldstein (Goldstein, N.I. et al, Clinical Cancer Research, 1: 1311-1318, 1995) is withdrawn in view of the amendment to the claims.

***Claim Rejections Maintained and New Grounds of Rejection:***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3, 24, 31-48 are/remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that

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was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the claims have been amended to include methods where a broad genus of “non-radiolabeled biological molecule inhibitor” that is a fragment of a monoclonal antibody that binds to EGFR that comprises a hypervariable region thereof.

Claim 1 and dependent claims 3, 24, 31-48 include within their scope claims to methods comprising treating a human patient with an effective amount of a combination of radiation and a non-radiolabeled biological molecule inhibitor of EGFR/Her-2, wherein the biological molecule inhibitor is a fragment of an antibody that binds to EGFR, where the fragment comprises a hypervariable region of the antibody. Claims 3, 24 and 31-48 refer to use of the antibodies, but because none of the dependent claims contain a limitation excluding the fragments recited in claim 1, these claims include within their scope methods comprising the administration of antibody fragments comprising a hypervariable region. The term “hypervariable region” is not a term of the art. However, the specification appears to define “hypervariable regions” as CDR regions (see page 15, line 11). Therefore, the phrase “a hypervariable region” may reasonably be interpreted to be the equivalent of a CDR region. The specification also provides the structures of the individual hypervariable regions of the C225 anti-EGFR antibody, but does not demonstrate that any of these regions binds to EGFR when it is out of the context of the antibody framework. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which heavy and light chain variable regions consists of three CDRs that

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provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity that is characteristic of a given antibody. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences, which maintain the required conformation of the CDRs, are required in order to produce a protein having antigen-binding function; and further, that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light chain variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff (Proc. Natl. Acad. Sci. USA, 79: 1979, 1982). Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibody fragments defined by the claims will bind to EGFR.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is for purposes of the ‘written description’ inquiry, “*whatever is now claimed*” (see page 1117). In the present case, the specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed.” (See Vas-Cath at page 1116.)

The claims are broadly drawn to methods comprising the use of any antibody that binds to EGFR and to the use of antibody fragments comprising as little as a single CDR from the antibody that binds to EGFR. In contrast the specification provides examples that are limited to

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demonstrating the effects of one anti-EGFR antibody, the C225 antibody. The specification also provides the structures of the CDR regions of the C225 antibody, but these structures are not representative of the full range of structures encompassed by the phrase “a fragment that comprises a hypervariable region” because the hypervariable region of the claimed methods may be from any anti-EGFR antibody. Furthermore, while the specification clearly demonstrates that the C225 antibody is effective in the treatment of human patients having cancer, the specification does not disclose any examples of antibody fragments that are as small as one CDR region that have the requisite binding specificity and also the anti-tumor effects of the C225 antibody. Thus, the specification has not disclosed even one species that might possibly be considered representative of the broad genus of antibody fragments comprising a single CDR region that also bind to EGFR.

For a claim drawn to a genus, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A “representative number of species” means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus (see Official Gazette 1241 OG 174, January 30, 2001). In the instant case, there does appear to be a substantial variation in the broad genus of antibody fragments that comprise one CDR where the



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antibody fragment is taken from an anti-EGFR antibody, because the individual CDR regions even within one antibody vary greatly in amino acid structure (see specification pages 15-16) and because the claims are broadly drawn to methods comprising the use of any anti-EGFR antibody and fragments thereof.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1,3, 24 and 31-48 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 11/206,825. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending 11/206,825 anticipate the claims of the instant case. The claims of the copending application are drawn to methods of inhibiting tumor growth comprising administering antibodies that bind to EGFR, at least one

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chemotherapeutic agent and radiation therapy. Thus, these claims are a species of the claims of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' remarks concerning the provisional double-patenting rejection are acknowledged. The rejection is maintained for the reasons of record.

### ***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran  
Patent Examiner  
March 19, 2007



LARRY R. HELMS, PH.D.  
SUPERVISORY PATENT EXAMINER